

Long-Term Risk of Recurrent Atrial Fibrillation as Documented by an Implantable Monitoring Device

Implications for Optimal Patient Care

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OBJECTIVES	The present study determined the incidence and time course of atrial fibrillation (AF) recurrences in patients with a history of AF and fitted with an implantable monitoring device.
BACKGROUND	The long-term risk of undetected recurrence of AF in patients receiving stable antiarrhythmic therapy remains uncertain.
METHODS	In 110 patients with a class I indication for physiologic pacing and a history of AF, a pacemaker with dedicated functions for AF detection and electrogram storage was implanted, and antiarrhythmic drug treatment was optimized. Patients were regularly followed up with evaluation of AF-related symptoms, a resting electrocardiogram (ECG), and interrogation of device memory. The incidence of AF recurrences lasting >48 h in asymptomatic patients presenting in sinus rhythm (SR) at the respective follow-up visit constituted the primary end point of this prospective study.
RESULTS	During 19 ± 11 months, 678 follow-up visits were performed. Atrial fibrillation was documented in 51 patients (46%) by ECG recording and in 97 patients (88%) by a review of stored electrograms ($p < 0.0001$). Device interrogation revealed AF recurrences lasting >48 h in 50 patients, 19 of whom (38%) were completely asymptomatic and in SR at subsequent follow-up. In 11 (16%) of 67 patients with device-confirmed freedom from AF for ≥ 3 months, AF lasting >48 h recurred subsequently.
CONCLUSIONS	This prospective study demonstrates a high incidence of recurrent AF despite optimized antiarrhythmic therapy. Of particular note, AF relapses >48 h remained totally asymptomatic in a significant proportion of patients. Freedom from AF for ≥ 3 months did not preclude subsequent long-lasting AF recurrence. (J Am Coll Cardiol 2004;43:47–52) © 2004 by the American College of Cardiology Foundation

Atrial fibrillation (AF), the most commonly encountered clinical arrhythmia, is associated with increased mortality and morbidity (1,2), largely due to thromboembolic complications, including ischemic stroke (3–5). Atrial fibrillation is often associated with typical symptoms such as palpitations, dyspnea, dizziness, and syncope (6–10), but a significant proportion of patients remain asymptomatic.

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Such clinically silent AF carries important prognostic implications, as recently emphasized in two large prospective trials on rate versus rhythm control in AF (11,12). The incidence of complications was higher in patients in whom sinus rhythm (SR) appeared to be restored and maintained compared with those who were subjected only to rate control. This finding may be related to episodes of undetected asymptomatic AF, which may keep patients at continued risk for stroke. The prevalence of asymptomatic

AF found incidentally on clinical examination is ~20% (13,14). Studies using Holter monitoring (15), transtelephonic monitoring (16,17), or event recorders (18) have reported an even higher prevalence. One study using implantable pacemakers for AF detection has reported an incidence of 50% of asymptomatic AF (19). However, this study was restricted to a one-month follow-up period, and the pacemakers did not have intracardiac electrogram storage capabilities for verification of atrial arrhythmias. Thus, the present prospective study aimed at the evaluation of AF recurrences, particularly asymptomatic ones, over a long observation period in patients fitted with a new implantable pacemaker with sophisticated arrhythmia documentation capabilities.

METHODS

Patient population. Patients were eligible for the study if they had a documented history of paroxysmal or persistent AF (at least 2 episodes in the previous 3 months), were available for long-term follow-up, and had a class I indication for physiologic pacing (sick sinus syndrome or atrioventricular [AV] block). Patients with permanent AF were excluded from the study. All patients gave written, informed consent. The study was approved by the institutional review

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Manuscript received June 17, 2003; revised manuscript received August 13, 2003, accepted August 26, 2003.

Abbreviations and Acronyms

AF	= atrial fibrillation
AV	= atrioventricular
ECG	= electrocardiogram/electrocardiographic
SR	= sinus rhythm

committee, and all procedures were in accordance with institutional guidelines.

Implantable monitoring device. All patients were implanted with an AT500 pacemaker capable of monitoring and treating AF (Medtronic, Inc., Minneapolis, Minnesota). This device offers a special algorithm for detection of atrial tachyarrhythmias, as described in detail elsewhere (20); the algorithm has been shown to have a sensitivity of 100% and a specificity of 98% for AF detection (21). Dedicated memory functions provide quantitative data, such as the number of detected AF episodes, the total time spent in AF since the previous follow-up visit, and the duration of each AF episode. Up to 35 stored individual AF episodes with atrial electrograms and marker/cycle length annotations allow verification of correct detection of the onset and end of each AF episode.

Study design. All patients were in SR at the time of pacemaker implantation. After implantation, device programming was performed, including activation of all AF-related memory functions. Devices were programmed to the DDD mode (lower rate limit 60 beats/min, upper rate limit 120 beats/min), with the rate response activated if chronotropic sinus node incompetence was present and with the AV delay programmed as long as necessary to allow spontaneous AV conduction in patients without AV block. For the purpose of this study, the dedicated algorithms of the device for prevention and termination of atrial tachyarrhythmias were not activated. The first device interrogation was performed one month after implantation with interrogation of all memory data; further device interrogations were scheduled at three and six months after implantation and at six-month intervals thereafter. Additionally, interim visits were performed as clinically indicated—for example, in the presence of symptoms. At each follow-up visit, a 12-lead resting electrocardiogram (ECG) and a telemetric ECG with simultaneous intracardiac recordings were obtained. Patients were also subjected to standardized interviews to verify the presence or absence of the most important AF-related symptoms (rapid and/or irregular heart beat, palpitations, dyspnea, syncope, or presyncope) (6–9) since the previous follow-up visit. Device-stored data were downloaded to diskette and subsequently analyzed by an investigator who was unaware of the patients' symptomatic status and findings on the follow-up ECG. Episodes of AF were printed out, and correct classification was verified by analysis of stored electrograms. Antiarrhythmic drug therapy was optimized if necessary over the first month after pacemaker implantation and maintained constant for the remainder of the study period. All patients were receiving oral anticoag-

Table 1. Patient Characteristics

Gender	
Female	47 (43%)
Male	63 (57%)
Type of AF (mutually exclusive)	
Paroxysmal	54 (49%)
Persistent	56 (51%)
Bradycardia	
Sick sinus syndrome	70 (64%)
AV block	40 (36%)
Cardiovascular disease	
Hypertension	70 (64%)
Coronary artery disease	51 (46%)
Valvular disease	36 (33%)
Cardiomyopathy	9 (8%)
None	18 (16%)
Echocardiographic parameters	
Left atrial diameter (mm)	47 ± 9
Left ventricular ejection fraction (%)	0.53 ± 0.14
Antiarrhythmic drug treatment	
Class I	4 (4%)
Beta-blockers	45 (41%)
Amiodarone	24 (22%)
Sotalol	20 (18%)
Calcium antagonists*	12 (11%)
Digitalis	18 (16%)
None	20 (18%)
Anticoagulation	
Coumadin (INR 2.0–3.0)	78 (71%)

*Only diltiazem and verapamil. Data are presented as the number (%) of patients or mean value ± SD.

AF = atrial fibrillation; AV = atrioventricular; INR = international normalized ratio.

ulation therapy (target International Normalized Ratio 2.0 to 3.0), except for those with contraindications and those in whom only short (<1 h) paroxysms of AF had been previously detected.

Study end points and statistics. The primary study end point was defined as the incidence of AF lasting >48 h, as documented by the implanted device in asymptomatic patients presenting in SR at the time of the follow-up visit. This duration was selected based on current guidelines (22), which recommend anticoagulation therapy to prevent thromboembolic complications in AF lasting >48 h. In patients whose stored electrograms documented that the true AF onset was not detected by the device but in whom intermittent atrial undersensing of small AF potentials was present, the daily cumulative time in AF during consecutive days was considered. If the patient experienced three consecutive days of AF for >20 h/day each, the AF episode was considered as one single, ongoing episode lasting >48 h with intermittent atrial undersensing. Secondary end points were the incidence of ECG- versus device-based documentation of AF and the incidence of AF lasting >48 h after freedom from AF for ≥3 months. Electrocardiogram-versus device-based documentation of AF was compared over time using Kaplan-Meier analysis, along with the Wilcoxon rank-sum test. The cumulative incidence of AF detection by devices versus ECG was compared using the

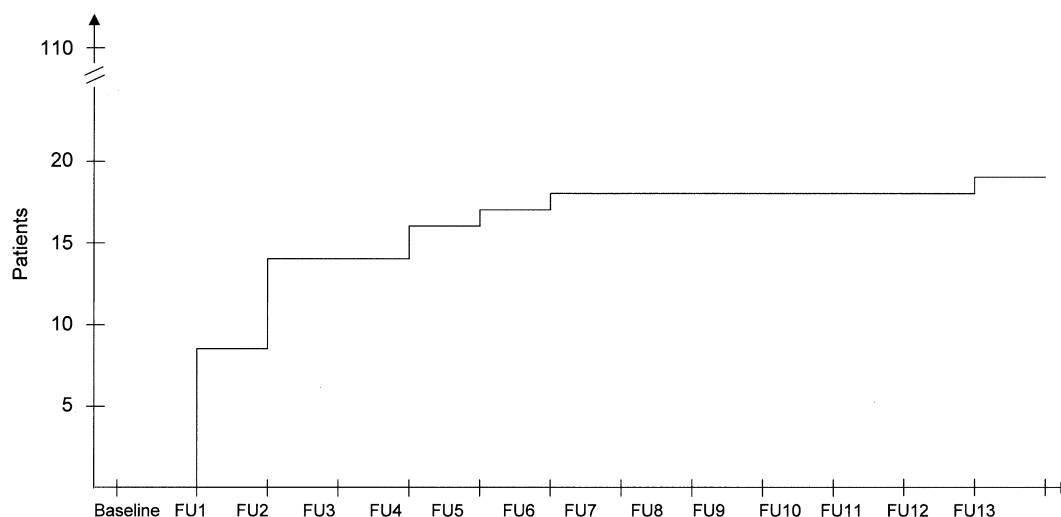


Figure 1. Cumulative incidence of asymptomatic atrial fibrillation recurrence >48 h not detected by serial electrocardiographic recordings during follow-up (FU) visits.

Fisher exact test. Statistical significance was assumed at $p < 0.05$.

RESULTS

Patient characteristics. A total of 110 patients were enrolled in the study: 63 men and 47 women (mean age 68 ± 9 years) (Table 1). Fifty-six patients (51%) had a history of persistent AF with at least one cardioversion attempt (range 1 to 6); the remainder had a history of paroxysmal AF. Seventy patients (64%) had AF associated with sick sinus syndrome. Bradycardia was drug-associated in 28 patients (25%). The most frequent underlying cardiovascular disease was hypertension. Coronary artery disease confirmed by angiography was present in 51 patients (46%) and lone AF in 16% of patients. A left atrial diameter >40 mm was documented in 79% of patients (>50 mm in 38%); left ventricular function was severely depressed (ejection fraction ≤ 0.35) in 24% of patients. All patients had clinical (age >65 years, hypertension, history of transient ischemic attack or stroke, diabetes, congestive heart failure, mitral stenosis) and/or echocardiographic (left atrial dilation, reduced left ventricular function) risk factors for stroke. Twelve patients had a history of stroke, transient ischemic attack, or peripheral embolism. Ninety patients (82%) received negative dromotropic drugs, mostly beta-blockers. Class I or III antiarrhythmic drugs were prescribed in 44% of patients. Seventy-eight patients (71%) were on oral anticoagulation, and 32 patients either had contraindications ($n = 10$), declined anticoagulation ($n = 12$), or had previously exhibited only short paroxysms of AF ($n = 10$). During the study period, 25 external cardioversions were performed in 18 patients.

Recurrence of AF during follow-up. Patients were followed for a mean of 19 ± 11 months (range 6 to 42), during which time a total of 678 follow-up visits took place (median 7 per patient [range 3 to 14]). With respect to

thromboembolic complications, there was one peripheral embolism in a patient not on anticoagulation. Bleeding complications were not observed.

Fifty patients had device-documented AF episodes lasting >48 h. Of these, 19 (38%) were asymptomatic and presented in SR at the respective follow-up visit (Fig. 1). Among patients with AF >48 h, no clinical or echocardiographic variables were predictive of the lack of symptoms; in particular, the percentage of patients with asymptomatic AF >48 h with a history of paroxysmal or persistent AF was identical (17% vs. 18%). In 51 (46%) of 110 patients, AF was documented by the resting ECG during follow-up, whereas device interrogation revealed episodes of AF in 97 patients (88%; $p < 0.0001$) (Fig. 2). In 57 patients (59% of patients with device-detected AF episodes and 52% of the total patient group), asymptomatic AF recurrence was detected in at least one follow-up period solely by the implanted monitoring device. Device-documented AF recurrence lasted >72 h in 42 patients (38%), >48 h in 50 patients (45%), >24 h in 58 patients (53%), and >12 h in 70 patients (64%). In 24 patients (22%), all recorded AF episodes were ≤ 12 h in duration (Fig. 3). In 44 patients (40%), AF-related symptoms were reported while the ECG and device memory showed absence of AF. Symptoms related to AF combined with ECG recordings at follow-up had a sensitivity of 68% and a specificity of 57% for AF detection.

Recurrence of AF after freedom from AF for ≥ 3 months.

Sixty patients (55%) were free of AF for ≥ 3 months, according to a lack of AF-related symptoms and documentation of SR at follow-up. Of these, 14 (23%) developed device-documented asymptomatic AF recurrence lasting >48 h during subsequent follow-up. In 67 (61%) of the 110 patients, device memory confirmed freedom from AF for ≥ 3 months. In 11 of these (16%), symptomatic or asymptomatic AF recurrences lasting >48 h were observed during

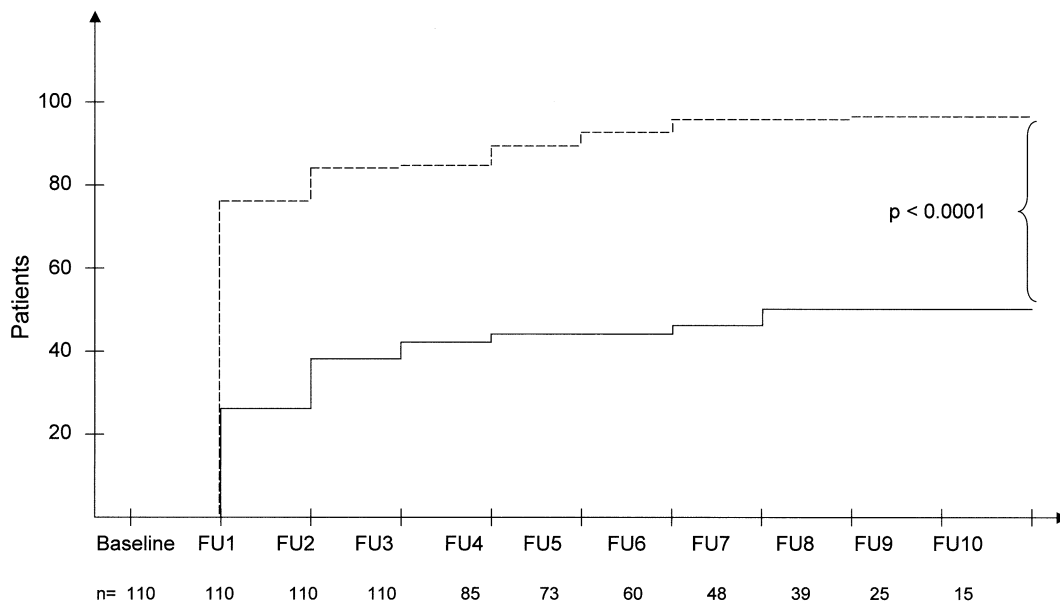


Figure 2. Cumulative incidence of detection of any atrial fibrillation recurrence by electrocardiographic recording during follow-up (FU) (solid line) versus information from the implanted device (dashed line). n = number of patients at risk.

further follow-up by continuous device monitoring. The longest period of freedom from AF before a device-documented AF recurrence >72 h was 20 months. There was no statistical relationship between any specific antiarrhythmic treatment regimen (beta-blockers, class III antiarrhythmic drugs, calcium antagonists, and digitalis) and the occurrence of asymptomatic AF episodes >48 h.

DISCUSSION

Main study findings. This prospective long-term follow-up study is the first to use continuous ECG monitoring by an implantable device for up to 42 months to document recurrences of AF and the exact duration of arrhythmia-free intervals and AF episode duration. It demonstrates that AF recurrences of >48-h duration are asymptomatic in more than one-third of patients with a history of paroxysmal or persistent AF. Moreover, in 16% of patients with a history of AF, recurrences of >48-h duration develop even after documentation of freedom from AF for three months or longer. These observations demonstrate that the

success rates of maintaining continuous SR in patients with a history of AF are often grossly overestimated. Our findings have important clinical implications for the treatment of patients with AF.

Prevalence of symptomatic AF. The majority of patients with AF documented by the implanted monitoring devices reported symptoms during the respective follow-up period. This is in agreement with previous studies correlating standard ECG recordings with symptoms suggestive of the presence of AF (7,13,14). However, the association between symptoms and AF is weak. Forty percent of patients in the present study reported symptoms suggestive of AF, but device interrogation proved the absence of AF during the respective follow-up period. Palpitations and perception of an irregular heart beat may also be caused by single or short runs of atrial premature beats, limiting the specificity and diagnostic reliability of symptoms potentially associated with AF. The wide variability in AF perception may also have constituted one reason for the lack of any difference in quality of life between patients assigned to rhythm versus rate control in prospective trials (11,23).

Prevalence of asymptomatic AF. Data on the prevalence of asymptomatic AF primarily depend on the method used for documentation. Studies using single or repeated surface ECG recordings obtained during a clinical visit found a prevalence of asymptomatic AF of 5% to 20% in unselected patient groups (7,13,14,24,25). Holter monitoring only slightly increases the diagnostic yield to detect asymptomatic AF (15,26). Event recorders can extend the monitoring duration up to one month but are unable to detect patients with silent AF if ECG storage is only triggered by patients' symptoms. Based on these diagnostic tools, the true recurrence rate of AF, particularly asymptomatic forms, remains

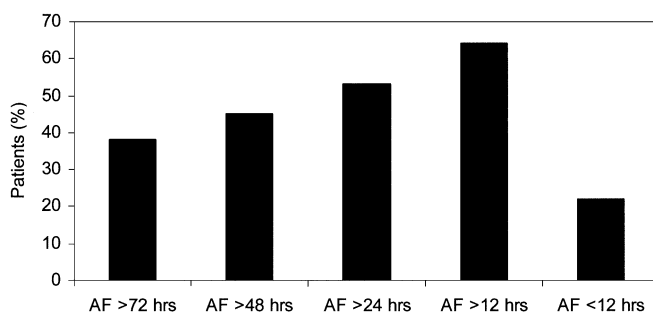


Figure 3. Prevalence of atrial fibrillation (AF) recurrences of various durations detected during follow-up.

uncertain. To reduce this diagnostic gap, event recorders that can automatically detect and store arrhythmias during a continuous monitoring period of seven days have been developed (18). Using this automatic storage mode, paroxysmal AF was diagnosed in 20 of 65 patients with recurrent palpitations and a negative 24-h Holter recording. Transtelephonic ECG transmission has been used to provide a “daily snapshot” of the atrial rhythm. In the Prevention of Atrial Fibrillation After Cardioversion (PAFAC) trial, 2,100 ECG recordings transmitted transtelephonically on a daily basis showed AF (17). Of these recordings, 75% were asymptomatic.

Implanted devices such as pacemakers or implantable cardioverter-defibrillators with atrial electrograms provide continuous rhythm monitoring and may thus enhance the diagnostic accuracy of detection of asymptomatic AF (27). This has been suggested in the Automatic Interpretation for Diagnostic Assistance (AIDA) trial, in which paroxysms of AF >1 min were recorded by the devices in half of the patients; 58% of these patients were completely asymptomatic (19). However, this study was limited by a short observation period of only 28 days and particularly by the lack of device-stored electrograms to prove the presence of AF. The present study is unique because it provides continuous atrial rhythm monitoring over a mean period of >18 months, using a highly sensitive and specific algorithm for AF detection. These data therefore provide fundamentally more accurate information on the occurrence of sustained asymptomatic AF than data derived from daily transtelephonic ECG transmissions of a few seconds only or event recording for one to two weeks. The present study demonstrates that asymptomatic AF escaped documentation by ECG recording during follow-up in 59% of patients. This emphasizes the underestimation of AF recurrences based solely on the evaluation of symptoms and repeated ECG recordings, which was demonstrated also in the subset of patients with AF recurrences lasting >48 h.

Clinical implications of asymptomatic AF. The underestimated prevalence of recurrent AF, particularly asymptomatic AF, in patients deemed to be successfully maintained in SR has obvious clinical implications. For instance, the efficacy of pharmacologic and nonpharmacologic treatment modalities (i.e., catheter ablation of AF) may be significantly overestimated in clinical studies, as well as in everyday clinical practice. The most apparent clinical implications of our findings relate to the need for anticoagulation in patients with AF. In the recently published Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, the lack of clinical benefit of the strategy of maintaining SR was partly due to the high incidence of stroke in patients believed to be in SR and in whom anticoagulation was subsequently withdrawn (11). The present study strongly supports the notion that according to current clinical guidelines (22) a significant proportion of patients with asymptomatic, undetected AF continue to be at increased risk for ischemic stroke after withdrawal of

anticoagulation. Even if “full disclosure” of the atrial rhythm is available (as realized by the implanted device in our study), 16% of patients free from any AF episode for ≥ 3 months developed persistent AF during further follow-up. Therefore, our findings reemphasize the conclusion drawn by the AFFIRM investigators (11) in that patients at increased risk for stroke should continue on anticoagulation even in the presence of seemingly stable SR.

Study limitations. All patients who received the implantable device with dedicated monitoring features for AF also had a class I indication for physiologic pacing. Therefore, the findings in our study apply to patients with bradycardia requiring pacing. However, it is likely that most of our observations can also be applied to patients with AF and antiarrhythmic drug treatment in the absence of bradycardia. Patients did not record their symptoms in a diary or use a manual activator that triggers device storage of symptoms. Therefore, some patients may not have been able to recall their symptoms during the follow-up visit. However, this corresponds to clinical routine follow-up care of patients with AF. The device used in the present study offers no information on the number of detected atrial or ventricular premature beats or short atrial runs which may have occurred and may explain symptoms in patients without detected AF episodes.

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